

# Chemesthesis and the Chemical Senses as Components of a “Chemofensor Complex”

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## Abstract

An important function of the chemical senses is to warn against dangerous biological and chemical agents in the environment. The discovery in recent years of “taste” receptor cells outside the oral cavity that appear to have protective functions has raised new questions about the nature and scope of the chemical senses in general and of chemesthesis in particular. The present paper briefly reviews these findings within the context of what is currently known about the body’s chemically sensitive protective mechanisms, including nonsensory processes that help to expel or neutralize threatening agents once they have been encountered. It is proposed that this array of defense mechanisms constitutes a “chemofensor complex” in which chemesthesis is the most ubiquitous, functionally diverse, and interactive chemosensory component.

**Key words:** airway, chemesthesis, chemoreceptors, gastrointestinal tract, immune system, olfaction, taste, trigeminal nerve

## Introduction

Life exists in a hostile environment: nutrients, water, and oxygen must all be obtained amid myriad physical and biological threats. Among these threats are toxins, bacteria, and chemical irritants that can enter the body during eating, drinking, breathing, or by contact with the skin. Once such agents enter the body, the first line of defense is the chemically sensitive receptors in the airway, alimentary canal, and dermis that serve olfaction, taste, and chemesthesis. By virtue of its ability to detect volatile chemicals in the air, olfaction plays the important exteroceptive role of sensing the odors of potential threats before their sources are encountered. In many mammalian species, these odors include the scents of predators (Blanchard et al. 2008), whereas in humans, the most important sentinel function of olfaction is to warn of sources of bacterial infection, such as rotting food or animal waste (Gudziol 1995). Olfaction also helps protect against chemical threats from man-made sources in the built environment, such as natural gas leaks and harmful industrial chemicals (Cain and Turk 1985; Cometto-Muniz et al. 2004; Dalton and Jaen 2010). Taste provides the essential enteroceptive function of detecting potential toxins (bitterness) or spoilage (sourness) in substances whose odors alone are not sufficiently repellent to prevent ingestion (Scott and Mark

1987; Glendinning 1994). Indeed, many toxic or irritant allelochemicals produced by plants for defensive purposes have tastes but not odors (Johns 1990). Chemesthesis (Green et al. 1990; Green and Lawless 1991), which derives in large part from chemically sensitive receptors of the senses of pain (Armstrong et al. 1953; Van Hees and Gybels 1972; Szolcsanyi 1977; Caterina et al. 1999; Jordt et al. 2004) and temperature (Hensel and Zotterman 1951; Green 1985; Schafer et al. 1986; Jordt et al. 2003; Nealen et al. 2003), has both exteroceptive and enteroceptive protective functions and provides the body with ubiquitous chemosensitivity. While it warns of airborne chemical irritants via sensory irritation of the eyes (Carstens et al. 1998; Cometto-Muniz et al. 2007) and nose (Cain et al. 2006), chemesthesis also signals the presence of chemical irritants in the epidermis (Green 2000) and the mucosal lining of the gastrointestinal tract (Boring 1915).

However, recent discoveries of “taste” receptors outside the mouth that appear to have a variety of sensory and nonsensory functions have raised new questions about the nature and scope of the body’s chemoreceptive defense mechanisms, and in particular those associated with chemesthesis. The present paper begins to address these questions by briefly reviewing the new discoveries in the context of other chemically sensitive

protective mechanisms, and by proposing a conceptual framework within which the functions of and relationships among these diverse mechanisms might be considered and further studied.

### Extraoral “taste” receptors

Functional G-protein-coupled receptors of the TAS1R and/or TAS2R families have been found in the airway mucosa (Finger et al. 2003; Gulbransen and Finger 2005; Deshpande et al. 2010; Tizzano et al. 2011), gastrointestinal tract (Wu et al. 2002; Margolskee et al. 2007), liver and pancreas (Taniguchi 2004), and even the brain (Ren et al. 2009). Although some of these receptors, notably TAS1Rs which in the mouth serve sweet and umami tastes, may play a role in nutrient sensing (Margolskee et al. 2007; Sclafani 2007; Egan and Margolskee 2008; Ren et al. 2009; Treesukosol et al. 2011), most receptors found in the airway and gut are TAS2Rs that appear to have protective functions against inhalation or ingestion of potentially harmful stimuli (e.g., Wu et al. 2002; Finger et al. 2003; Glendinning et al. 2008; Sternini et al. 2008; Hao et al. 2009; Sbarbati et al. 2010; Tizzano et al. 2010). The best studied of these are the solitary chemoreceptor cells (SCCs), which were first identified in fish (Finger 1997; Sbarbati et al. 1998). SCCs were unknown in adult mammals until their discovery in murine nasal mucosa by Finger et al. (2003). Nasal SCCs have been shown to express functional taste-related G-protein-coupled receptors of the TAS2R family, which in the taste system respond selectively to bitter-tasting stimuli. These cells appear to mediate the apnea response to inhaled aerosols of denatonium benzoate via synaptic connections with the trigeminal nerve (Gulbransen et al. 2008; Silver and Finger 2009; Tizzano et al. 2010). It was also recently demonstrated that some nasal SCCs respond to acyl-homoserine lactones, which are quorum-sensing signals produced by Gram-negative bacteria (Tizzano et al. 2010). Because nasal SCCs communicate with the trigeminal nerve, the sensitivity to acyl-homoserine lactones demonstrates that, as had recently been proposed (Sbarbati et al. 2009), bacterial infections of the nasal mucosa can be sensed directly via the nervous system. The ability of nasal SCCs to respond to high concentrations of odorants and chemical irritants also firmly implicates them as contributors to nasal chemosensory irritation (Lin et al. 2008), and SCCs in the larynx and trachea are likely contributors to cough, apnea, and other protective respiratory reflexes (Kinnamon 2011; Tizzano et al. 2011) that are triggered via the vagus nerve. All of these properties qualify upper airway SCCs as newly identified and functionally important components of chemesthesia.

However, TAS2Rs in non-gustatory epithelia do not always communicate directly with nerves (Behrens and Meyerhof 2011; Kinnamon 2011). Some SCCs in the nose are not innervated by the trigeminal nerve, and most TAS2Rs in the lower airway and gut are expressed in cells that have no direct connection to visceral nerves (Wu et al. 2002; Rozengurt and Sternini 2007; Sternini et al. 2008; Behrens and Meyerhof

2010; Deshpande et al. 2010; Sbarbati et al. 2010; Tizzano et al. 2011). Such cells may be more precisely described as “nonsensory chemoreceptor cells” (NCCs). Rather than evoking sensations or neurally mediated reflexes, stimulating these cells initiates protective physiological or humoral responses. In the human lung, TAS2Rs are expressed in motile cilia that help sweep harmful chemicals, particles, and microbes from the airways (Shah et al. 2009), whereas others may induce a calcium-dependent relaxation of airway smooth muscle that may help flush invading toxins via bronchodilation (Deshpande et al. 2010; see, however, Belvisi et al. 2011; Morice et al. 2011). In the gastrointestinal tract, TAS2Rs have been identified in enteroendocrine cells that when stimulated by denatonium lead to the release of cytokines that include CCK, a peptide that slows gastric emptying and motility (Chen et al. 2006; Sternini et al. 2008). Slower gastric emptying after ingestion of poisons may help lower their toxicity by reducing the rate of uptake (Wicks et al. 2005; Glendinning et al. 2008). In addition, intragastric infusion of bitter-tasting stimuli in rodents can produce conditioned flavor aversions that protect against future ingestion of foods or substances that contain poisons or pathogens (Glendinning et al. 2008). Evidence that the vagus nerve is activated by intragastric infusions of denatonium benzoate (Uneyama et al. 2004) raises the possibility that some TAS2Rs in the stomach do communicate directly with the nervous system. However, Glendinning et al. (2008) showed that reductions in the lick rate for a palatable solution became significant only after several minutes of intragastric infusion of the bitter-tasting ligand. Such a slow change in behavior suggests the conditioned aversions are mediated through a humoral mechanism, or via a humoral-sensory interaction (Hao et al. 2008; Behrens and Meyerhof 2011), rather than by a direct sensory mechanism. The sensory status of TAS2Rs in the gut therefore remains unclear.

Whether or not they have sensory effectors, SCCs and all other extraoral “taste” receptors have been described as comprising a “Diffuse Chemosensory System” (Sbarbati and Osculati 2005; Sbarbati et al. 2010). While this designation draws attention to the wide distribution and functional diversity of taste-related G-protein-coupled chemoreceptors, it is not clear whether these receptors together qualify as a sensory system. There is at present no evidence that SCCs in different anatomical regions are linked by either a neural or a humoral network, and NCCs are not, by definition, sensory receptors. It may be more useful to consider functional G-protein-coupled receptors in different tissues and organs as specialized chemical sensors, some of which may serve ingestive or metabolic functions while others have protective functions, and that how the signals from the sensors are used or transmitted depends upon their specific function. For example, because chemoreceptors located at the body’s interface with the environment serve exteroceptive appetitive or sentinel functions, rapid signaling via the nervous system facilitates acquisition or avoidance of chemical

stimuli. In contrast, chemoreceptors that lie deeper within the body serve enteroceptive protective or metabolic functions that generally act more slowly via physiological or humoral mechanisms.

### The immune system and chemesthesia

The most important of the body's chemically sensitive defense systems is, of course, the immune system. Although most chemoreception in the immune system is in the form of humoral or cell-to-cell signaling (Kalish 1995), some components of the immune response involve close interactions with chemosensory receptors of the cutaneous and visceral nerves that contribute to chemesthesia. The evidence that SCCs in the nasal mucosa can detect acyl-homoserine lactones (Tizzano et al. 2010) is a new and particularly interesting example of such an interaction. In that case, SCCs provide a sensory signal of bacterial invasion via the trigeminal nerve that triggers defensive and expulsive responses (e.g., apnea, sneezing), while immune cells identify and attack the bacteria directly. More complex interactions take place as part of the inflammatory response to pathogens. Inflammation resulting from bacterial infection causes immune cells to release proinflammatory cytokines, some of which, such as bradykinin and histamine, are also ligands for sensory receptors of the pain system (Jancso et al. 1985; Rang et al. 1991; Sikand et al. 2009; Akiyama et al. 2010). Consequently, an increase in the production and release of these cytokines not only increases blood flow and plasma extravasation but also contributes to the development of hyperalgesia by sensitizing chemically sensitive nociceptors (e.g., Jancso et al. 1980; Kessler et al. 1992; Caterina et al. 2000; Bautista et al. 2006). Furthermore, many of the chemically sensitive nociceptors themselves release vasoactive cytokines (e.g., substance P, CGRP), which can in turn contribute to the inflammatory response (Wallengren 1990; Kowalski et al. 1997). However, immune cells also have the capacity to release opioid peptides, which have a quelling (analgesic) effect on the nociceptors that mediate inflammatory pain (Stein 1995; Rittner et al. 2003; Rittner and Stein 2005; Liou et al. 2011). The immune system and chemically sensitive receptors of the pain system therefore interact dynamically to regulate the vascular and sensory components of the inflammatory response to pathogens.

Some of the same nociceptors that mediate inflammatory pain also participate in the exteroceptive sentinel function of chemesthesia. Most notably, the transient receptor potential channels TRPV1 and TRPA1, which are expressed in nociceptors and respond to cytokines and other inflammatory factors (Caterina et al. 2000; Bessac and Jordt 2008; Dhaka et al. 2009), also respond to a variety of environmental irritants and allergens (Bautista et al. 2006; Bessac and Jordt 2008). Thus, chemically sensitive nociceptors in the skin and mucus membranes serve both to signal contact with irritants and allergens and to initiate nascent inflammatory responses which,

if exposure continues, grow in proportion to the nature and magnitude of the environmental threats. This remarkably close biochemical and functional relationship between the immune system and the chemical sensitivity of the pain system prompted Blalock (1984; Blalock and Smith 2007) to describe the immune system as "the sixth sense."

### The chemofensor complex

Thus it is clear that humans and other mammals have an array of chemically sensitive defense mechanisms in addition to those provided by the traditional chemical senses of taste and smell. However, because these mechanisms are both sensory and nonsensory in nature and because some interact while others do not, they cannot be considered part of a unified system. Such a diverse group of defensive mechanisms might be more aptly described as a "chemofensor complex" (chemo + fensor, from the Latin, "defensor") which comprises a variety of chemoreceptors that are adapted to serve different protective functions in different regions and organs of the body.

The components of the chemofensor complex as currently conceived and their anatomical distributions are listed in Table 1 according to their primary roles in avoiding, expelling, or attacking threatening chemical and biological agents. Specifically, olfaction, taste, and chemesthesia all provide sensory signals that help avoid inhalation, ingestion, or absorption of potentially dangerous substances, and chemesthesia additionally serves as the sensory trigger of expulsive reflexes, such as sneeze and cough. NCCs and the immune system function primarily to expel or attack chemical and biological threats that either go undetected by chemosensory mechanisms or cannot be successfully avoided.

This conceptual framework may prove particularly useful for stimulating and guiding further study of the protective functions of chemesthesia, including its interactions with the immune system (Blalock 2005; Caceres et al. 2009) and its mediation, in large part, by the afferent pathways that encode chemical pain and itch (Green 1990; Sikand et al. 2009;

**Table 1** The components of the chemofensor complex and their anatomical distribution

Component	Nose	Oral cavity	Upper airway	Lower airway	GI tract	Skin
Olfaction	X	—	—	—	—	—
Taste	—	X	—	—	—	—
Chemesthesia	X	X	X	X	X	X
NCC <sup>a</sup>	—	—	X	X	? <sup>b</sup>	—
Immune system	X	X	X	X	X	X

"X" indicates a component is present in the specified region.

<sup>a</sup>Nonsensory chemoreceptor cells.

<sup>b</sup>It is unclear whether cells expressing T2Rs in the GI tract communicate directly with visceral nerves or function as NCCs (see text).

Klein et al. 2011). Other important and promising areas of study in which progress is already being made include the chemosensory mechanisms of apnea (Tizzano et al. 2011), sneeze (Widdicombe 1982), and cough (Breslin et al. 2001; Bessac and Jordt 2008; Peyrot des et al. 2011), and the possible contributions of chemosensory cells in different regions of the alimentary canal to the nausea, discomfort, and visceral pain (Wicks et al. 2005; Peyrot des et al. 2011) that can result from ingestion of poisons, toxic allelochemicals, and disease-causing bacteria. Thus, just as there is evidence that extraoral and extranasal chemoreceptors play a role in regulating the appetitive processes of food intake and metabolism (Margolskee et al. 2007; Sclafani 2007; Egan and Margolskee 2008; Ren et al. 2009; Treesukosol et al. 2011), chemoreception outside the traditionally defined chemical senses also plays a vital role in protecting the body against chemical and biological threats encountered in both the natural and the built environment.

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